Improving delivery of malaria treatments

Professor David Schellenberg, Director of the ACT Consortium, discusses their work to improve the way artemisinin-based combination therapies are used to treat malaria, as well as the challenges they face working across 10 different countries

What are the overall goals of the ACT Consortium?

The overall aim of the ACT Consortium is to improve the way in which artemisinin-based combination therapies (ACTs) are used to treat malaria. ACTs are recommended by the World Health Organization (WHO) as the first-line treatment for *Plasmodium falciparum* malaria, the cause of the vast majority of malaria deaths.

Although ACTs have been increasingly used over the past 10 years, questions remain on how to improve access to them. It is a sad reality that the majority of people who are infected with malaria do not have access to ACTs. Conversely, many who take these drugs do not actually have malaria! There is clearly a need to improve the targeting of ACTs to patients who have the parasites.

Despite the widespread use of ACTs and their approval by regulatory authorities, relatively little is known about their safety profile, especially in certain risk groups. For example, there may be an unacceptable adverse event profile in people living with HIV, or interactions with the antiretroviral drugs they take. In addition, in some settings, people may take three or more courses of ACTs in a one-year period, even though the safety of such repeat dosing has not been formally evaluated.

Finally, we are investigating issues around quality. Recent years have seen concern growing about substandard ACTs in malaria-endemic countries. This may be a result of poor manufacturing processes, degradation or counterfeiting of these drugs.

How are you working to achieve these goals?

The Consortium is looking into approaches to improve access to malaria treatment through the use of community health workers and by exploring the potential role of the private retail sector in making ACTs available. In order to explore approaches to improve drug targeting, we are conducting eight cluster randomised trials – the most rigorous approach possible for the evaluation of a public health intervention.

All ACT Consortium studies that generated safety data have channelled them into an industry standard database for detection of adverse effects, hosted by the Liverpool School of Tropical Medicine. A related series of studies has evaluated the changes in blood concentrations of drugs when co-administering antiretrovirals and ACTs.

What is your background in malaria research, and how did it lead you to your current position?

I began my work on malaria in East Africa in the mid-1990s, evaluating drugs and vaccines for malaria prevention and treatment. A trial of a drug-based approach to preventing malaria called Intermittent Preventive Treatment in Infants (IPTi) showed particular promise as a new component of some malaria control strategies. We went on to develop, implement and evaluate a strategy to deploy IPTi through the routine health system in southern Tanzania – this provided me with first-hand experience of the challenges of delivering malaria control.

The ACT Consortium works across 10 different countries, primarily in sub-Saharan Africa. How different do your approaches have to be across such an array of social, political and scientific backgrounds?

Product developers go to great lengths to ensure that new medicines are safe and efficacious. However, it is then necessary to ensure that these medicines reach the patients who need them. This requires functioning supply chains, adequate stock-management and appropriate health-seeking behaviour by patients.

When patients go to their care givers, they need to have a parasitological diagnosis of malaria, followed by prescription of the appropriate dose of the correct drug, with advice on how best to take it. Many of these factors vary considerably from one setting to another. In some countries, 70 per cent of people live more than 15 km from a health facility. In such settings, community health workers and private retail outlets are more important.

In order to introduce diagnostic tests, it is essential to ensure that training materials and courses are provided. We have adopted a variety of approaches in different countries to ensure that appropriate materials are available. For most of the studies, extensive formative research was conducted to inform the development of the strategies to support deployment of ACTs and rapid diagnostic tests (RDTs).

Do you envisage the Consortium's work influencing policy in the future?

So far, we have contributed to the discussion about the role of RDTs in the private sector; involving ourselves in policy decisions and further work considering operational issues around their deployment.

The greatest short-term gains resulting from ACT Consortium efforts are likely to be a result of the programmatic implications of our findings. For example, the various tools – training materials and related documentation – which have been developed to support the introduction of RDTs. These are available on our website – www.actconsortium.org/resources.

A **combined** effort

The **ACT Consortium** sponsors 25 research projects across 10 countries. By addressing four key research themes, the Consortium hopes to provide sorely needed evidence for policy makers and end the suffering caused by malaria

THE SUCCESSFUL CONTROL of malaria is largely dependent on treatment with effective drugs. Artemisinin-based combination therapy (ACT) is the current gold standard of treatment for *Plasmodium falciparum* malaria, the most common cause of severe malaria worldwide. Despite their widespread use, there are few evidence-based guidelines to direct the deployment of ACTs.

The ACT Consortium is a global research partnership comprising eminent public health and academic institutions across Africa, Asia, Europe and the US. It studies most aspects of ACT implementation, and uses interdisciplinary approaches to do so. By conducting research around four key themes, the Consortium aims to answer questions surrounding malaria drug delivery, which will in turn enable policy makers and programme implementers to make more informed decisions.

TARGETING

www.actconsortium.org/targeting

Although the World Health Organization (WHO) recommends prescribing ACTs only to those patients who test positive for malaria – with a rapid diagnostic test (RDT), for example – over-diagnosis is endemic in Africa. Treating the majority of the population may have been appropriate when a high proportion of fever cases were due to malaria, and when drugs were inexpensive, widely available and had a good safety track record. But these factors have now changed, and this approach wastes precious ACTs.

The solution lies in the widespread use of sensitive and specific RDTs. To evaluate the feasibility of strategies based on RDTs to improve ACT targeting, the Consortium conducted eight cluster randomised trials. One such trial, in Uganda, involved two groups of registered drug shops, which often represent the only source of treatment for patients. One group continued to sell treatments based on symptoms, while the other used RDTs and only sold treatments to those who tested positive for malaria.

RDTs proved popular amongst drug shop owners, who felt professional pride in being part of the healthcare system, and customers, who perceived an improvement in their treatment. Most importantly, compliance with the test results was high – less than 2 per cent of those with a negative result received ACTs. The Consortium has presented these results to national policy makers who are considering a scale-up of the intervention to promote the rational and correct use of ACTs on a national level.

ACCESS

www.actconsortium.org/access

Barriers present at every stage in the care pathway mean that only a small proportion of those who require antimalarial medication actually receive it. Many resort to informal care where, if they receive a drug at all, it may be ineffective or provided in an inadequate dose. Research shows that in some places 80 per cent of people receiving private sector ACTs do not actually have malaria; while only around 30 per cent of people with malaria are receiving these drugs.

The Consortium's IMPACT2 project addressed this desperate need for improved access by evaluating the Affordable Medicines Facility – malaria (AMFm) in Tanzania, an initiative which distributed subsidised ACTs throughout both public and private facilities. The initiative successfully decreased the price of ACTs in the private sector from over US $5 to under $1, leading to an increase in their availability and market share. Although IMPACT2 showed this sort of subsidy can make a major step forward in improving access to medication, the full solution requires the systematic introduction of diagnostics in the private sector to target ACTs more effectively.

QUALITY

www.actconsortium.org/quality

Reliable and high quality medication is of course crucial for the effective treatment of malaria. Unfortunately, counterfeit and substandard ACTs are presenting a serious threat. Their early detection is imperative, but there is currently no efficient approach to do so in Africa.

To address this, the ACT Consortium established a project to obtain robust estimates of the frequency of counterfeit, substandard and degraded ACTs in Africa, as well as other regions covered by the Consortium. They are also working to combine epidemiology and analytical chemistry so that they can be confident that the drug samples being processed are representative of the bigger picture. In the long term, the project will continue to liaise with international donors and the pharmaceutical industry, as well as national health ministries, to ensure the quality of drugs used to treat malaria.

THE WORK OF THE ACT CONSORTIUM

OBJECTIVES

To sponsor research studies throughout malaria-endemic regions worldwide in an effort to answer key questions concerning the delivery of artemisinin-based combination therapy (ACT) – the first-line treatment recommended by the World Health Organization (WHO) for severe malaria.

PARTNERS

US Centers for Disease Control and Prevention (CDC), Georgia, USA • **Georgia Institute of Technology**, Georgia, USA • **University of California, San Francisco**, USA • **Liverpool School of Tropical Medicine**, UK • **London School of Hygiene and Tropical Medicine**, UK • **University of Copenhagen**, Denmark • **Karolinska Institutet**, Sweden • **Ifakara Health Institute**, Tanzania • **Kilimanjaro Christian Medical Centre**, Tanzania • **National Institute for Medical Research**, Tanzania • **National Malaria Control Programme**, Tanzania • **Ghana Health Service**, Ghana • **Kintampo Health Research Centre**, Ghana • **Makerere University**, Uganda • **Ministry of Health**, Uganda • **University of Yaoundé**, Cameroon • **Zanzibar Malaria Control Program**, Zanzibar • **University of Cape Town**, South Africa • **College of Medicine, University of Malawi**, Malawi • **College of Medicine, University of Nigeria**, Nigeria • **Health Protection and Research Organisation**, Afghanistan • **Healthnet**, Afghanistan • **Merlin**, Afghanistan • **National Malaria Control Programme**, Cambodia

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PROFESSOR DAVID SCHELLENBERG has been Director of the ACT Consortium since 2009, and is also Professor of Malaria and International Health at the London School of Hygiene & Tropical Medicine.

SAFETY

www.actconsortium.org/safety

Clinical trials are crucial in the process of deciding whether an antimalarial drug is safe. However, they may miss rare – but potentially serious – adverse effects. WHO recommends the use of ACTs for malaria and antiretroviral combination therapy (ART) for HIV/AIDS. Currently there is a serious knowledge gap regarding interactions between ACTs and antiretroviral medications.

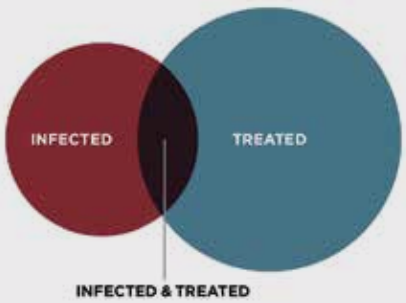
The 'Interactions between ACT and antiretrovirals in co-infected patients (InterACT)' project set out to understand better the relationship between these two therapies, in terms of their safety, efficacy and pharmacokinetics. The clinical study followed the progress of HIV patients in Tanzania being treated for malaria with a common type of ACT called artemether-lumefantrine (AL). Despite evidence that the drugs interfere with each other – altering their blood concentrations – preliminary findings show that treatment with AL works equally effectively and with no additional side-effects in HIV patients. This reassures that the use of both drug types can continue to be fully recommended in treatment guidelines.

ARTEMISININ-BASED COMBINATION THERAPY (ACT)

- Most effective treatment for *P. falciparum* malaria (recommended by WHO)
- Consists of artemisinin-based compounds in combination with other classes of antimalarials – this reduces the likelihood of resistance
- Introduced in response to parasite resistance to previous treatments
- The artemisinin component kills most of the parasites at the beginning of treatment, whilst the partner drug clears the remainder

RAPID DIAGNOSTIC TESTS (RDTs)

- WHO-recommended tools that assist in the diagnosis of malaria by detecting malaria parasites in blood
- The backbone of efforts to increase access to malaria diagnosis
- Have rapidly increased in availability and use (40 per cent of all cases tested in the WHO African region in 2012)
- Cost around US $0.50 each
- Do not require electricity or qualified health professionals



Explore www.actconsortium.org/VennGeneratorTool to illustrate the extent to which malaria treatment is targeted to malaria patients.

IMPACT

Since the beginning of its research projects in 2008, the ACT Consortium has stimulated and influenced discussion about RDTs – providing important information to both the Roll Back Malaria (RBM) Partnership and the Global Fund. In the future they expect to provide further advisory committees with the evidence they need to make recommendations. The immediate impact of the Consortium's research, however, is likely to come from the extensive tools and guidelines they have developed and evaluated to support the introduction of RDTs.

The Consortium is now approaching the end of its 25 studies in 10 countries. Professor David Schellenberg, Director of the ACT Consortium, is enthusiastic about what the future holds: "We are at an exciting point, as almost all studies have completed data collection; and analyses and writing are at fever pitch. In the coming year, we anticipate a series of important results on how best to deploy RDTs". The future for the improved targeting of malaria treatment looks very promising.

For research updates visit **www.actconsortium.org/projects**